DOES THE D_3 DOPAMINE RECEPTOR (D_3r)PLAY A ROLE IN ADDICTION?

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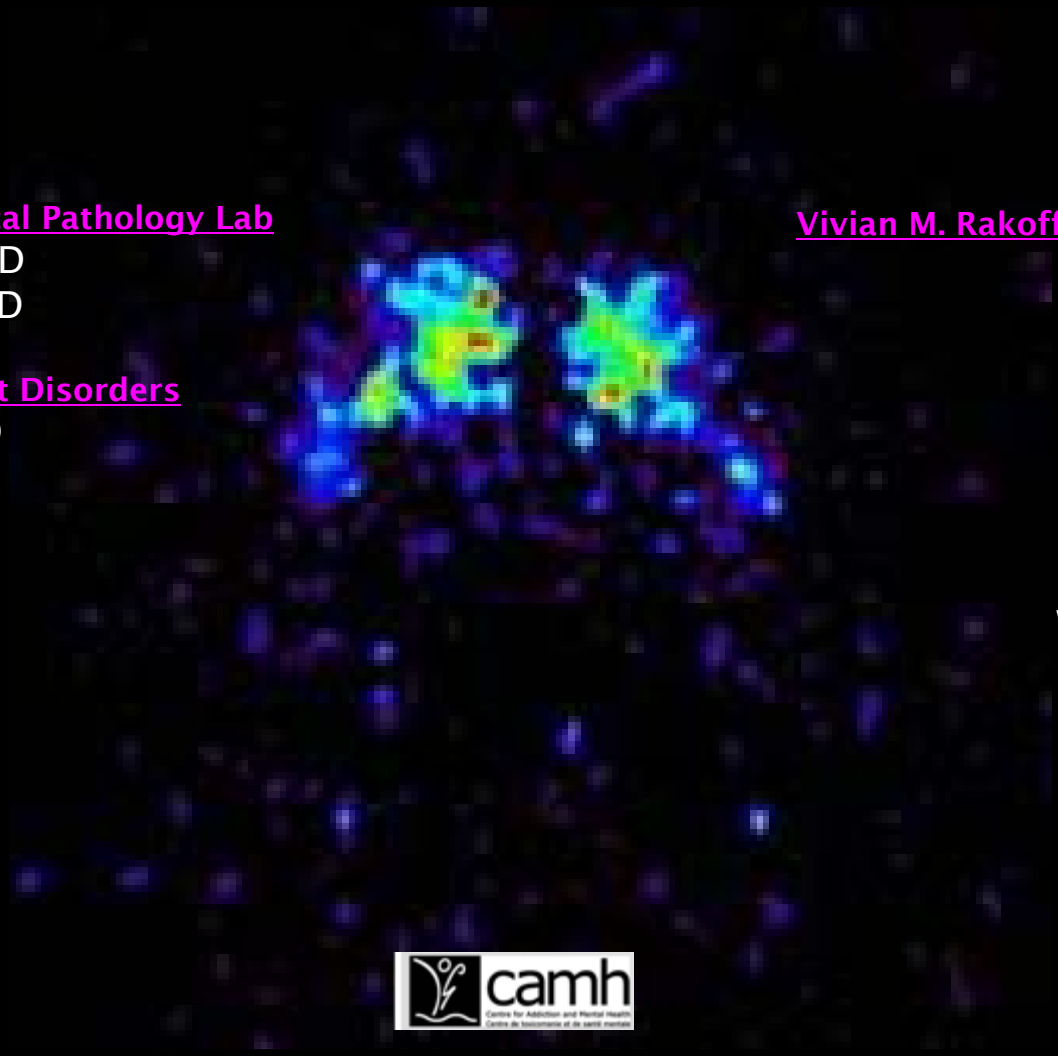
camh

Acknowledgments

Human Neurochemical Pathology Lab
Stephen J. Kish, PhD
Jun Chao Tong, PhD

Centre for Movement Disorders
Mark Guttman, MD
John Adams, MD

Alanna Sheinberg
Jill Burkeholder



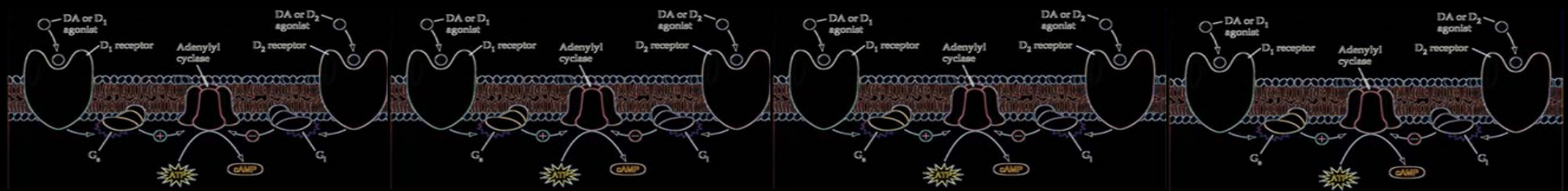
Vivian M. Rakoff PET Imaging Centre
Sylvain Houle, MD
Alan Wilson, PhD
Pablo Rusjan, PhD

Alvina Ng
Jeannie Fong
Armando Garcia
Winston Stableford
Min Wong
Tina McCluske

Funding:
CIHR, OMHF

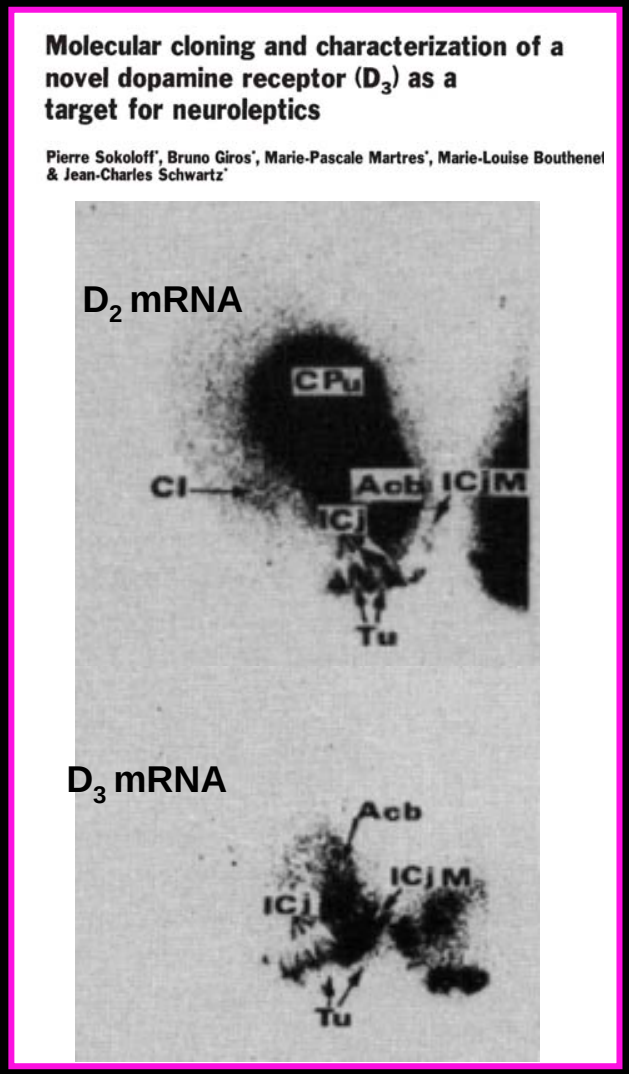
Overview

- Investigating the role of the DA D_3 receptor in humans - D_3 in Addiction / Impulse control disorder (ICD)
- PART I The D_3r system: What is special about it?
- PART II D_2 and D_3r levels are differentially affected by changes in DA levels
- PART III Rational that the D_3r could be involved in addiction
- PART IV Preliminary data on the D_3r in stimulant users
- PART V Status of the D_3r in patients with PD who gamble



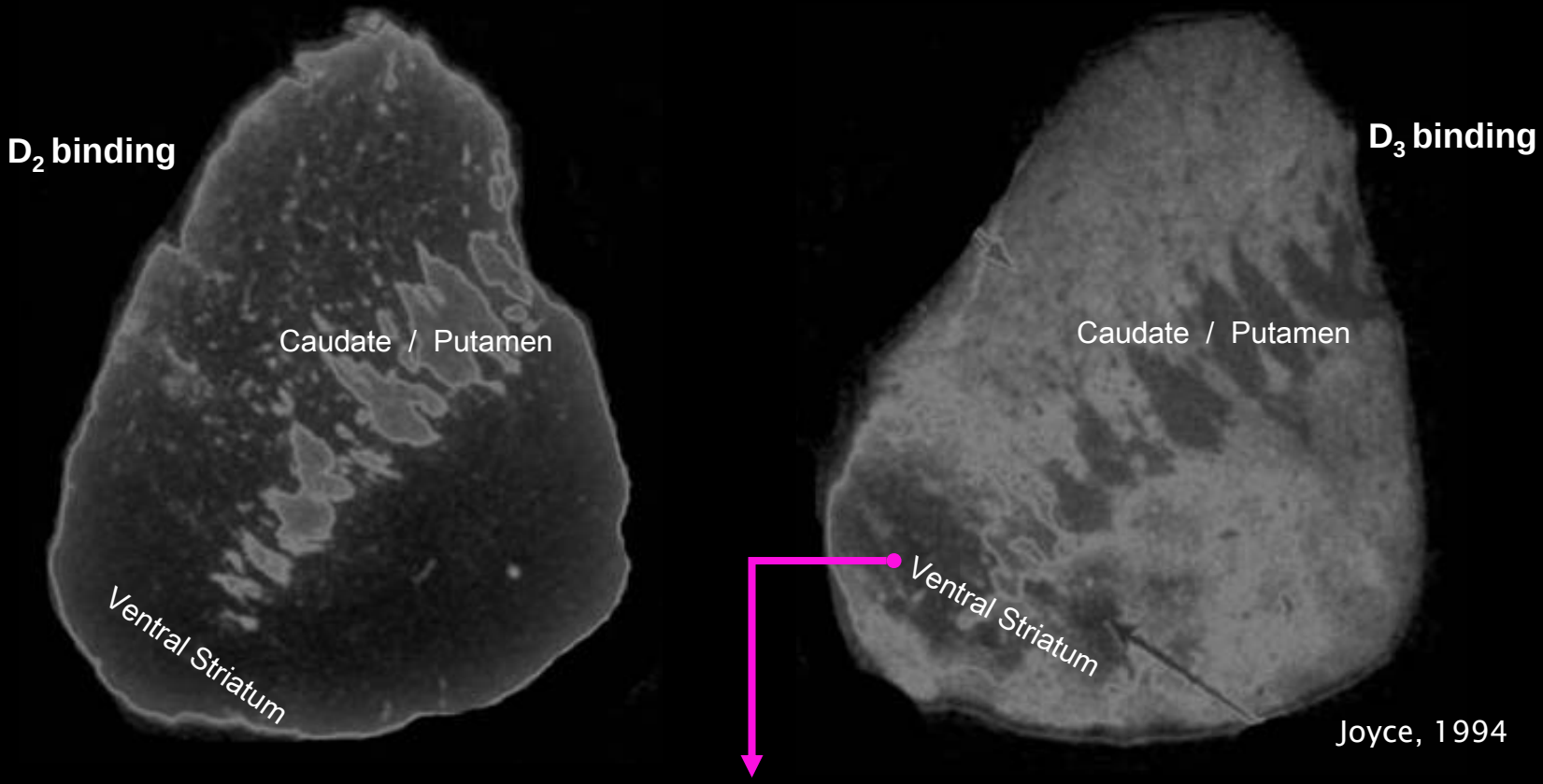
I

What is special about the D_3R?



- $D_3 \neq D_2$ (and D_1): pharmacology, transduction system & ANATOMY
- Overall the D_3 out numbered by the D_2 (2X)
- D_2: High expression in whole striatum (mesocortical system)
- D_3: lower expression DC /DP
- D_3: high expression in ventral (limbic) striatum, Island of Calleja, septum and nucleus basalis (mesolimbic system)

The D_3 Limbic Localization: Cognitive / Motivational / Emotional Function?



The Dopamine D3 Receptor: A Therapeutic Target for the Treatment of Neuropsychiatric Disorders

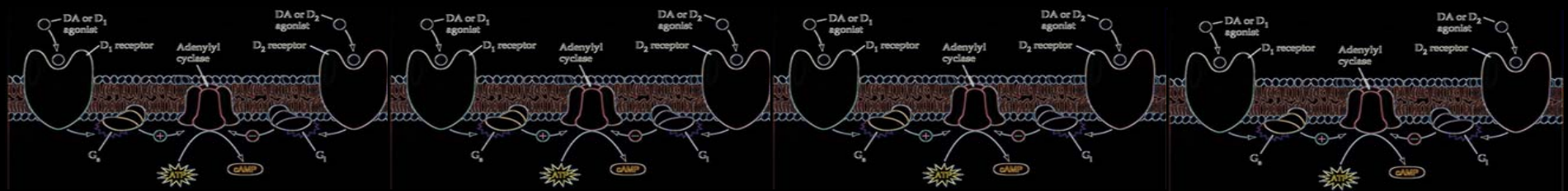
pp.25-43 (19) **Authors:** *L. Leriche, E. Bezard, C. Gross, O. Guillin, B. L. Foll, J. Diaz, P. Sokoloff*

Sign in

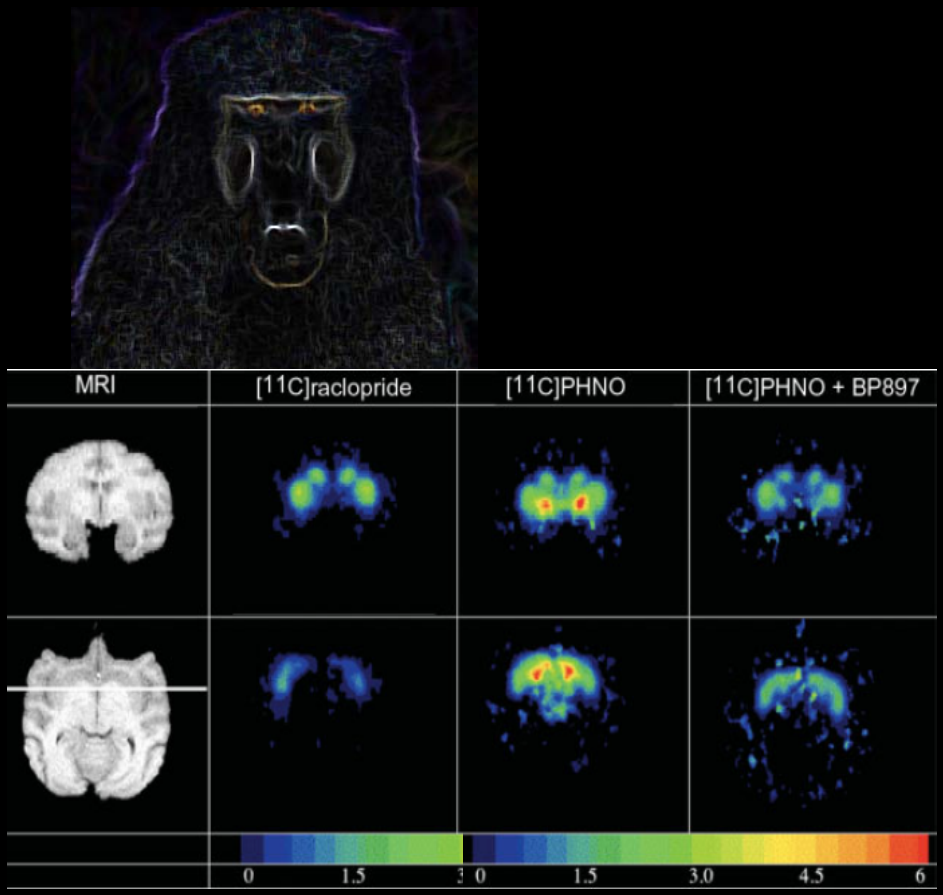
Abstract

Elusive Role of the D_3

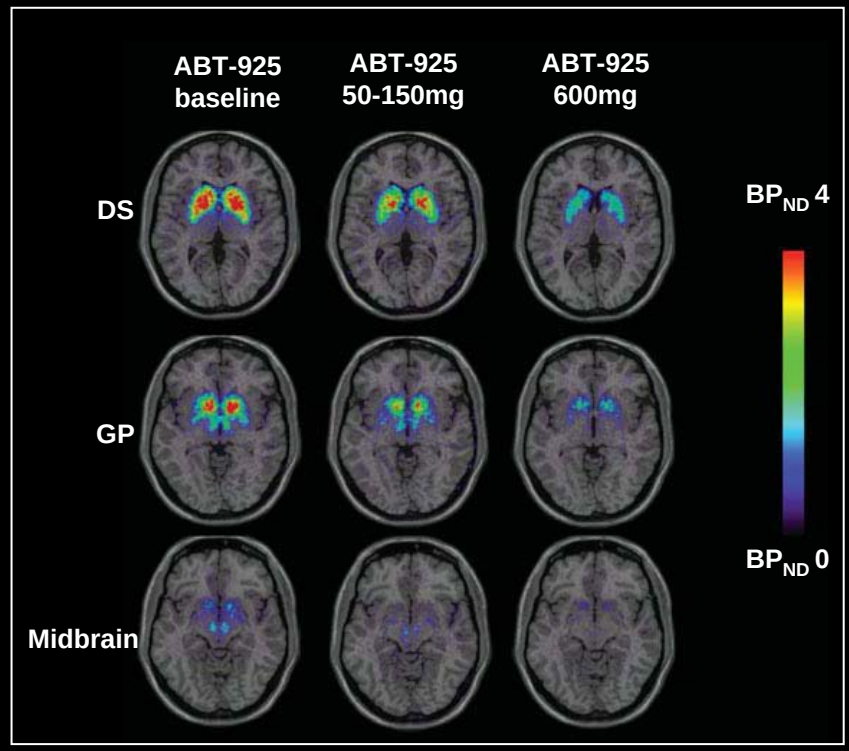
- The role of the D_3r in humans remains largely elusive
- Lack of research tools (Radioligands, Antibodie, Specific pharmacological agents, Knock-out mice)
- Possible to study D_3r binding in humans *in vivo* with PET



Investigating D_3 with PET



Narendran, 2007



Graff-Guerrero, 2009

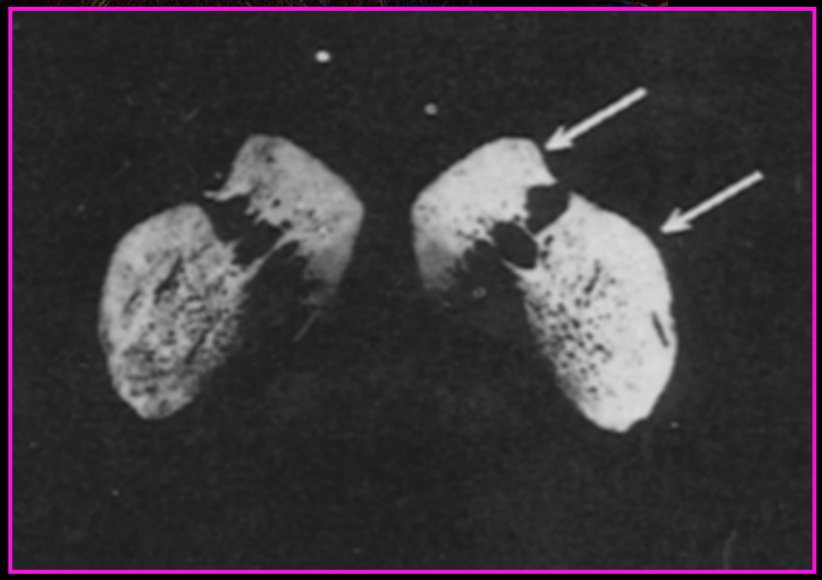
- (+)[^{11}C]PHNO a full $D_{2/3}$ receptor agonist PET tracer – and a D_3 preferring ligand
- Bio-distribution is consistent with D_3 in humans
- Binding blocked by D_3 antagonist

II

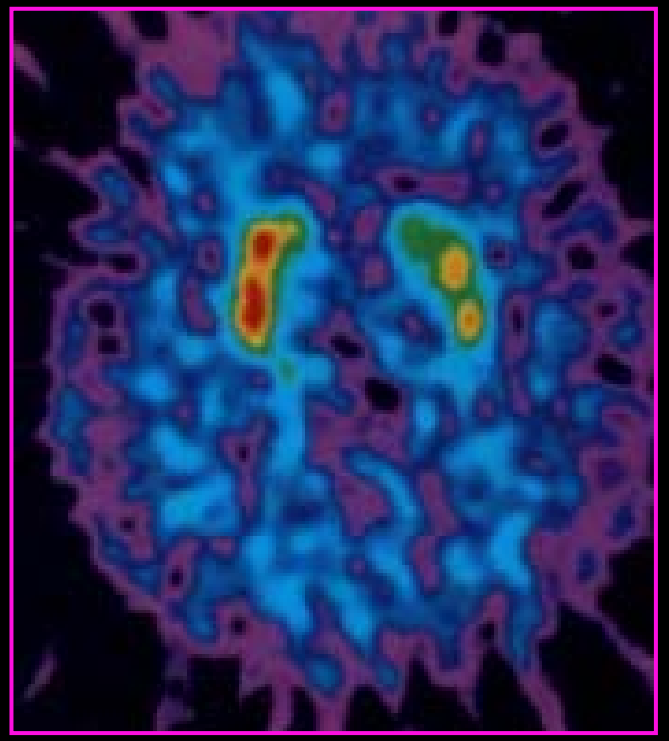
D_3 vs. D_2 response to Changes in DA levels

- D_3 vs. D_2 respond differently to DA depletion
- COMPLETELY counters the concept of denervation supersensitivity

D_2 is UP in PD!

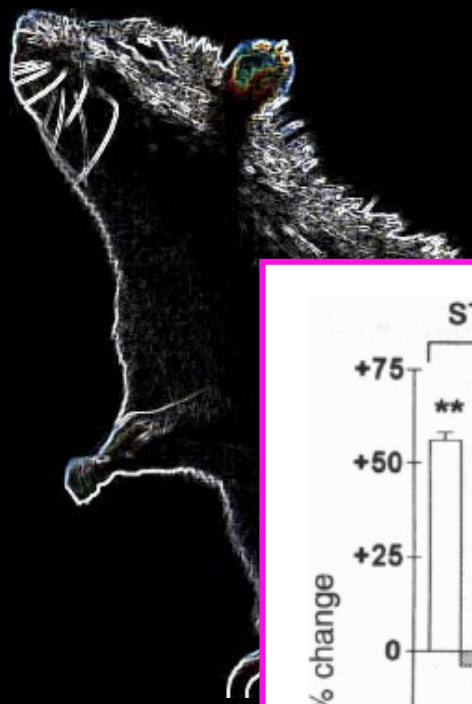


Increased [H^3}Sulipride in MPTP treated monkey
(Graham, 1990)

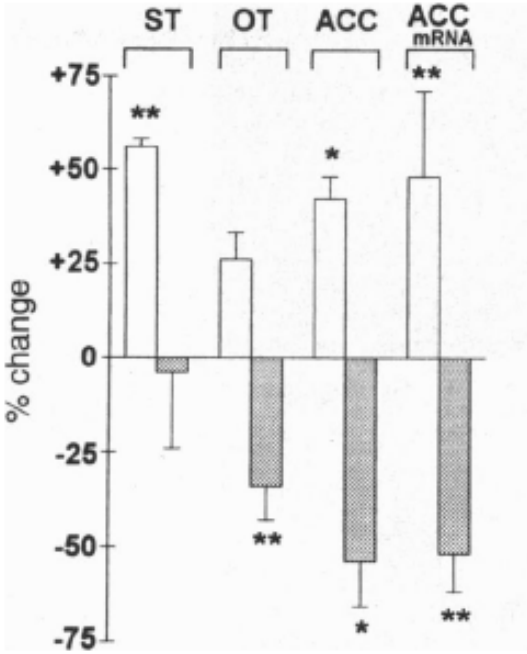


Increased [^{11}C]Raclopride in PD
(**Rinne, 1995)**

Paradoxically D_3 is DOWN!



Diaz, 1995



Changes in striatal dopamine D3 receptor regulation during expression of and recovery from MPTP-induced parkinsonism

T.V. Wade, D.S. Rothblat, J.S. Schneider*

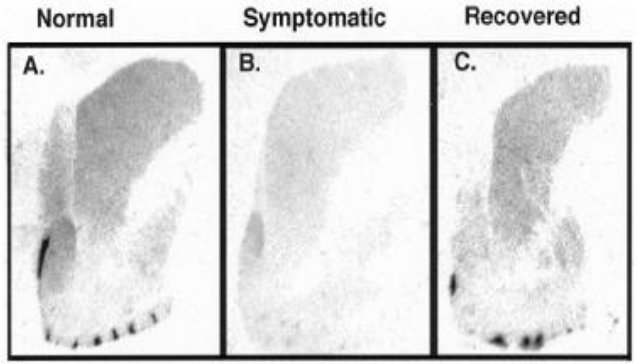


Fig. 1. Autoradiograms of total [^{3}H]-7OH-DPAT binding to D3 receptors in the striatum of normal (A), symptomatic (B) and recovered (C) animals. Significant decreases in binding were observed in all striatal subregions between normal and symptomatic animals, while no significant changes in binding were observed between normal and recovered animals.

Q.: Do striatal D_3r in human behave the same way as they do in animal studies chronically depleted of DA?

STUDY I Objective: to compare D_3 vs D_2 binding in drug-naïve PD and controls

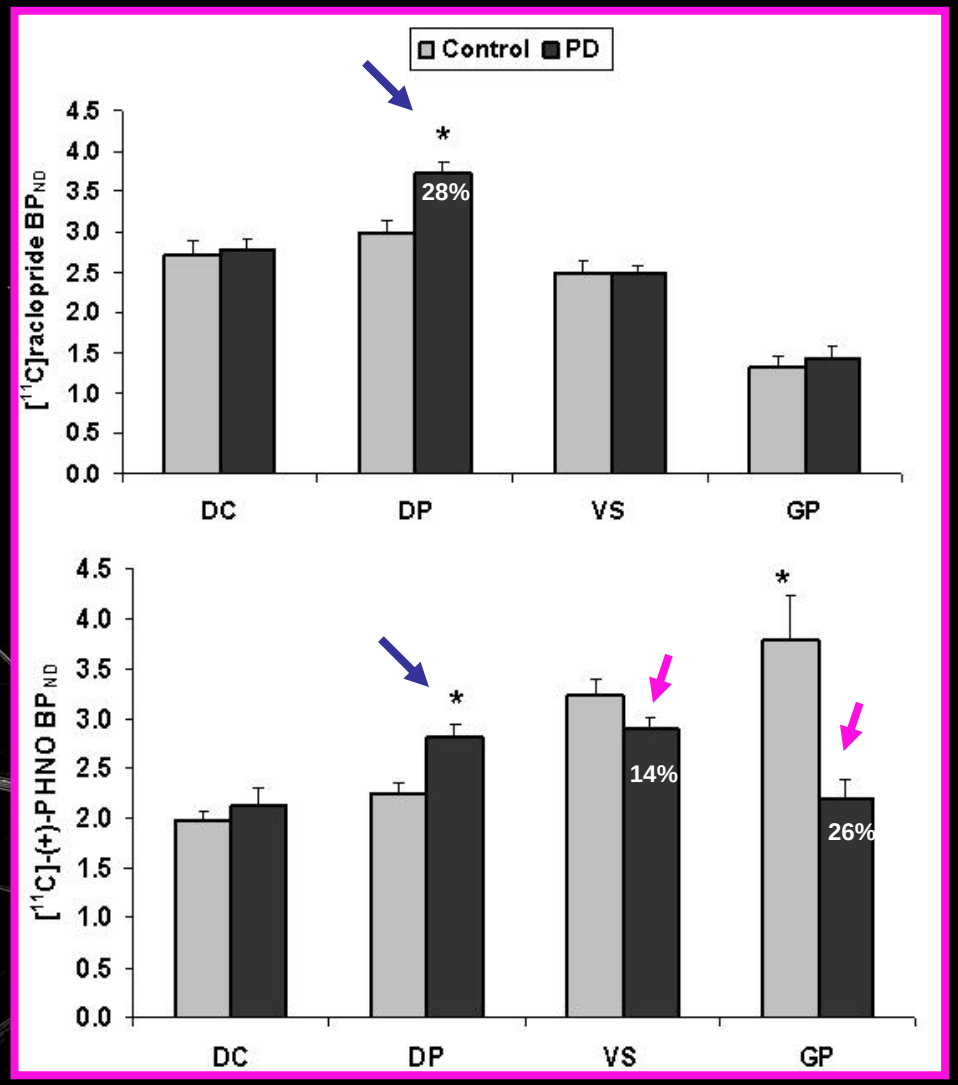
Hypothesis:

D_2r ([^{11}C]raclopride binding) = UP-REGULATED in never treated patients with PD;

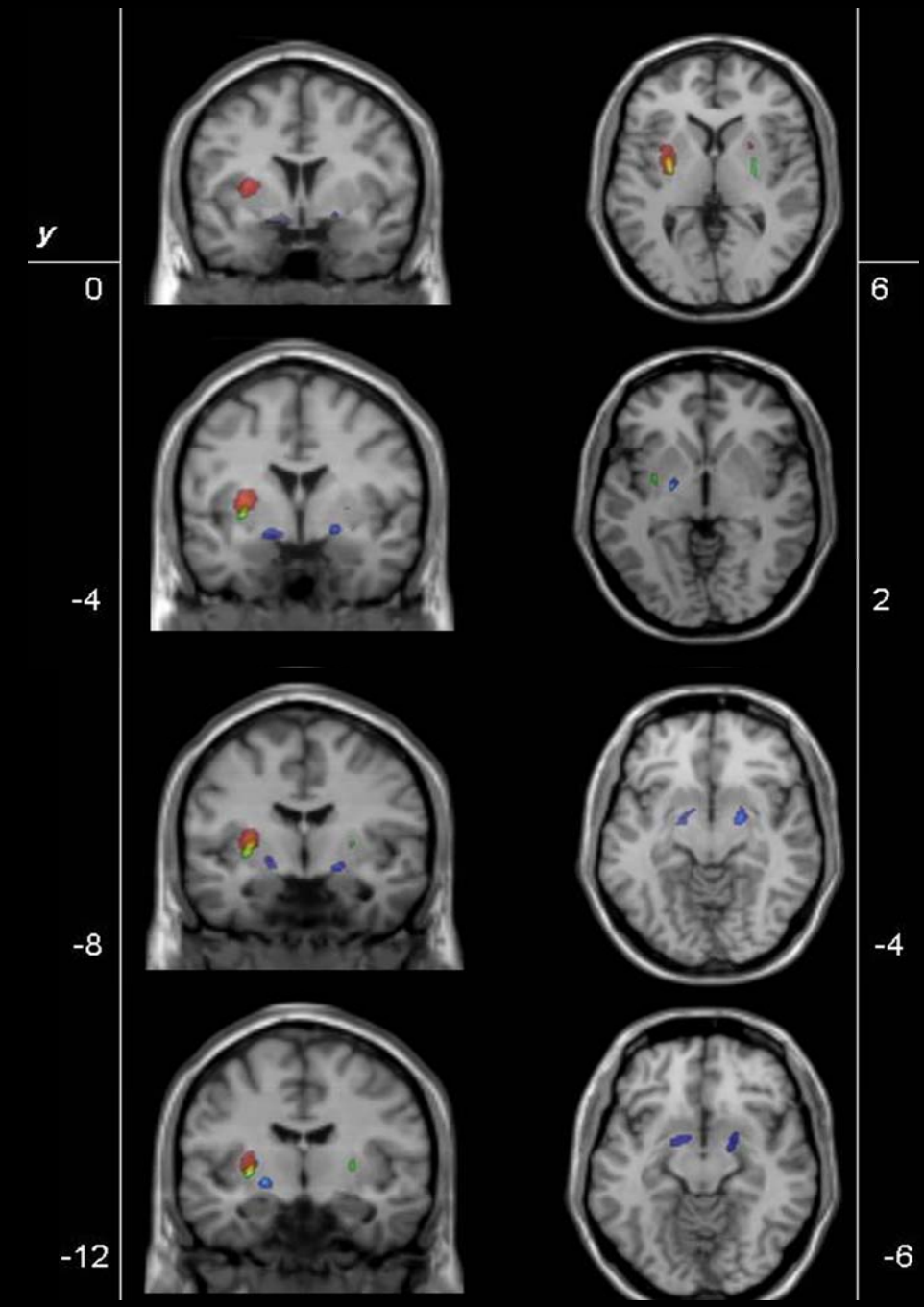
D_3r ([^{11}C](+)PHNO binding) = DOWN REGULATED.

PD patients have DECREASED D_3 binding and INCREASED D_2 binding

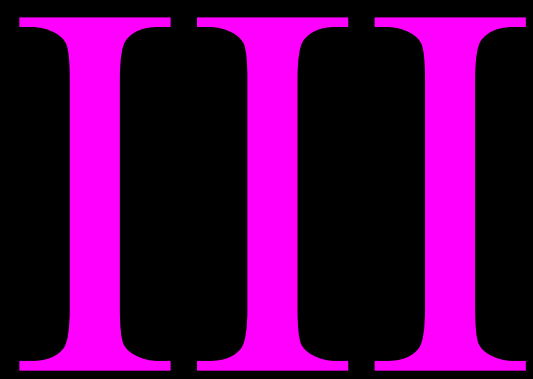
Subjects: 10 de-novo PD 10 controls
Scans with [^{11}C]raclopride and [^{11}C](+)PHNO



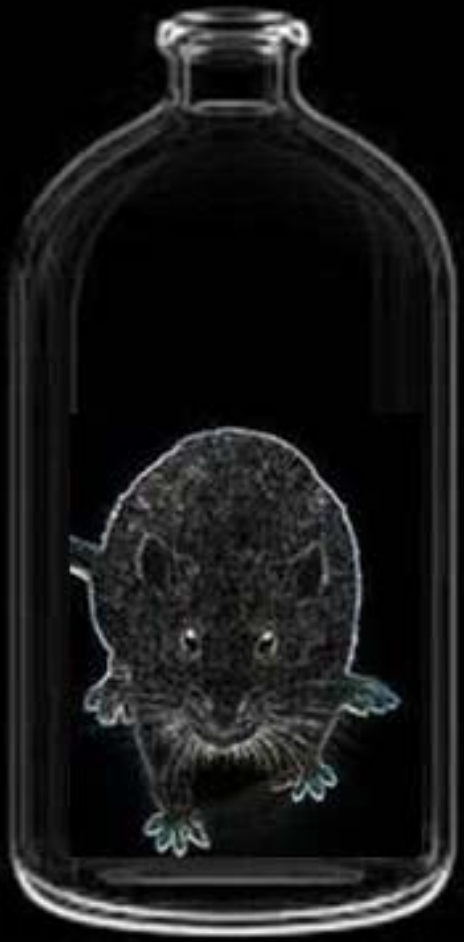
t-maps



(+)[^{11}C]PHNO BP_{ND} PD > Control
[^{11}C]raclopride BP_{ND} PD > Control
(+)[^{11}C]PHNO BP_{ND} PD < Control

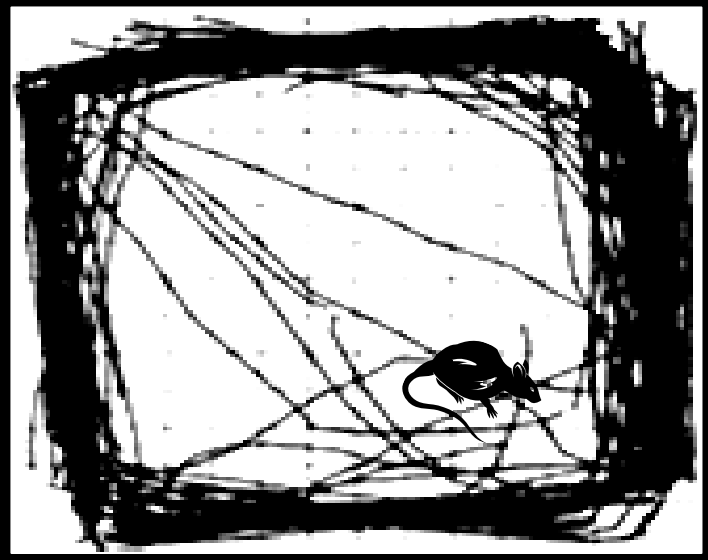


D_3r level is increased after repeated DAergic stimulation



- ≠D_2 and the D_1 r
- D_3r is ↑ after repeated DAergic stimulation
- Related to Sensitization to DA agonist

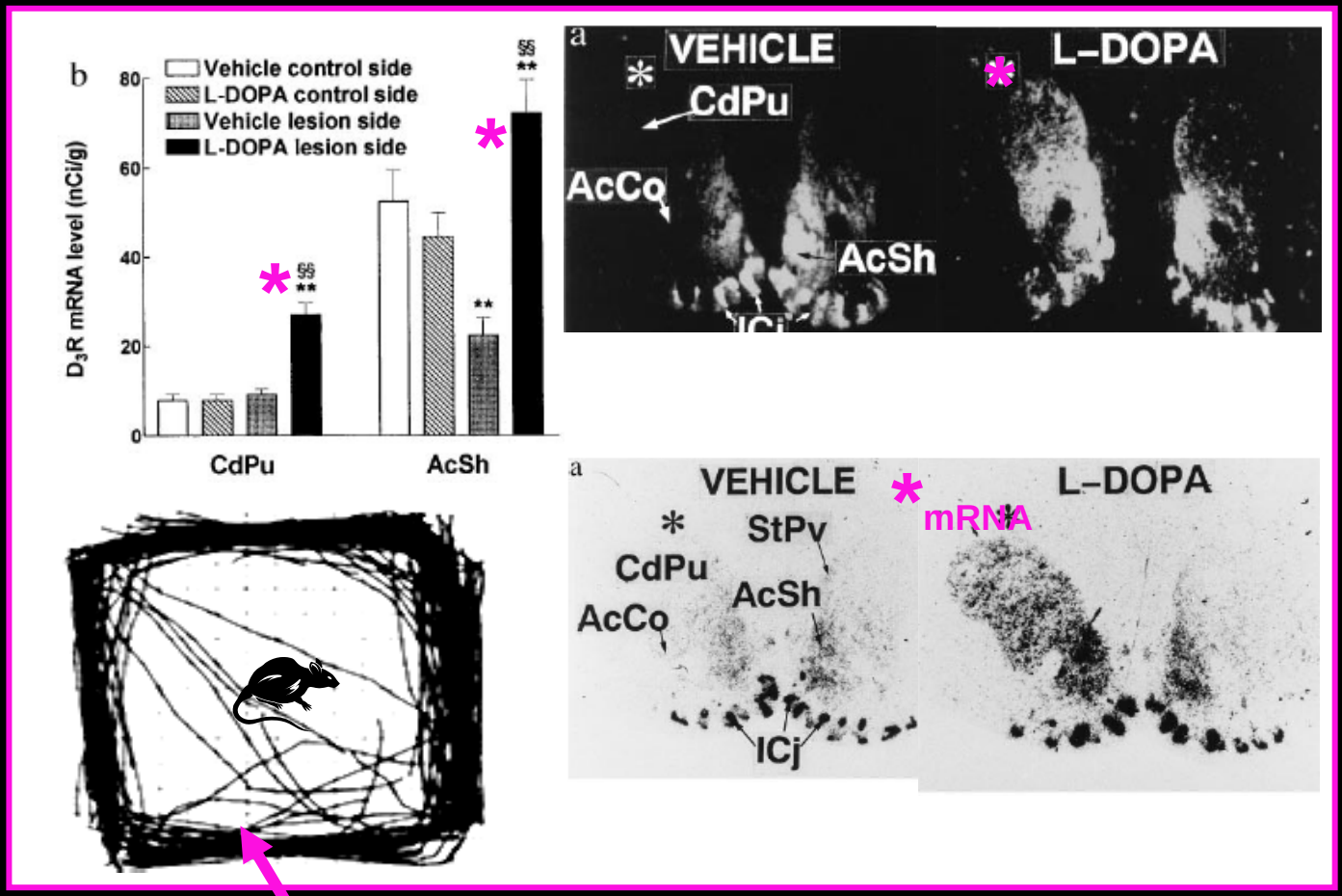
Sensitization: model of addiction



- Repeated DAergic stimulation = greater sensitivity to the effects of the drug (motor activity);

- ↑ response to cues associated with a rewarding response

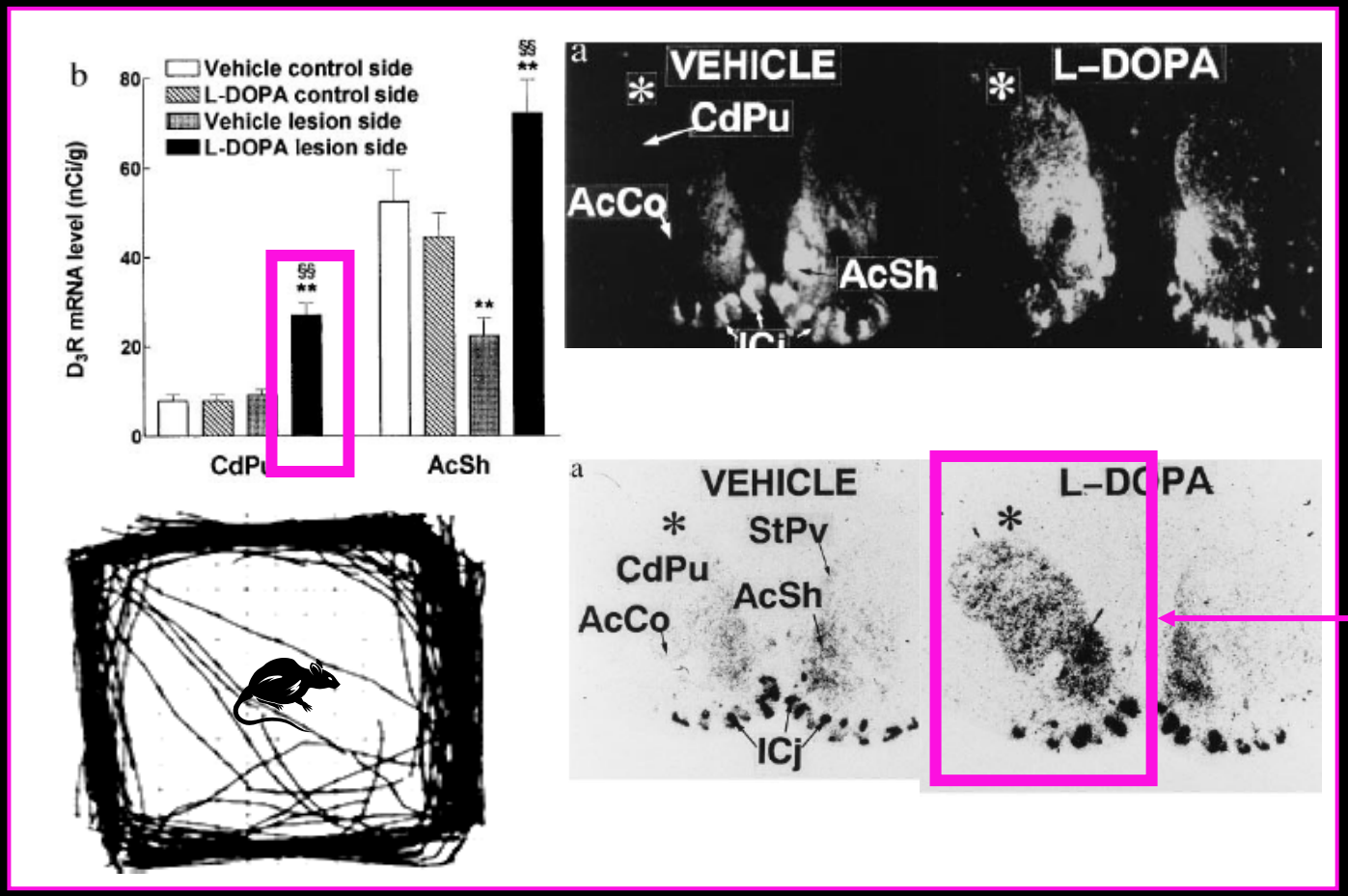
Repeated DAergic stimulation Leads to an OVER EXPRESSION of D_3



Bordet, 1997

Related to BEHAVIORAL SENSITIZATION

Changes also Occur in the Dorsal Striatum!



Bordet, 1997

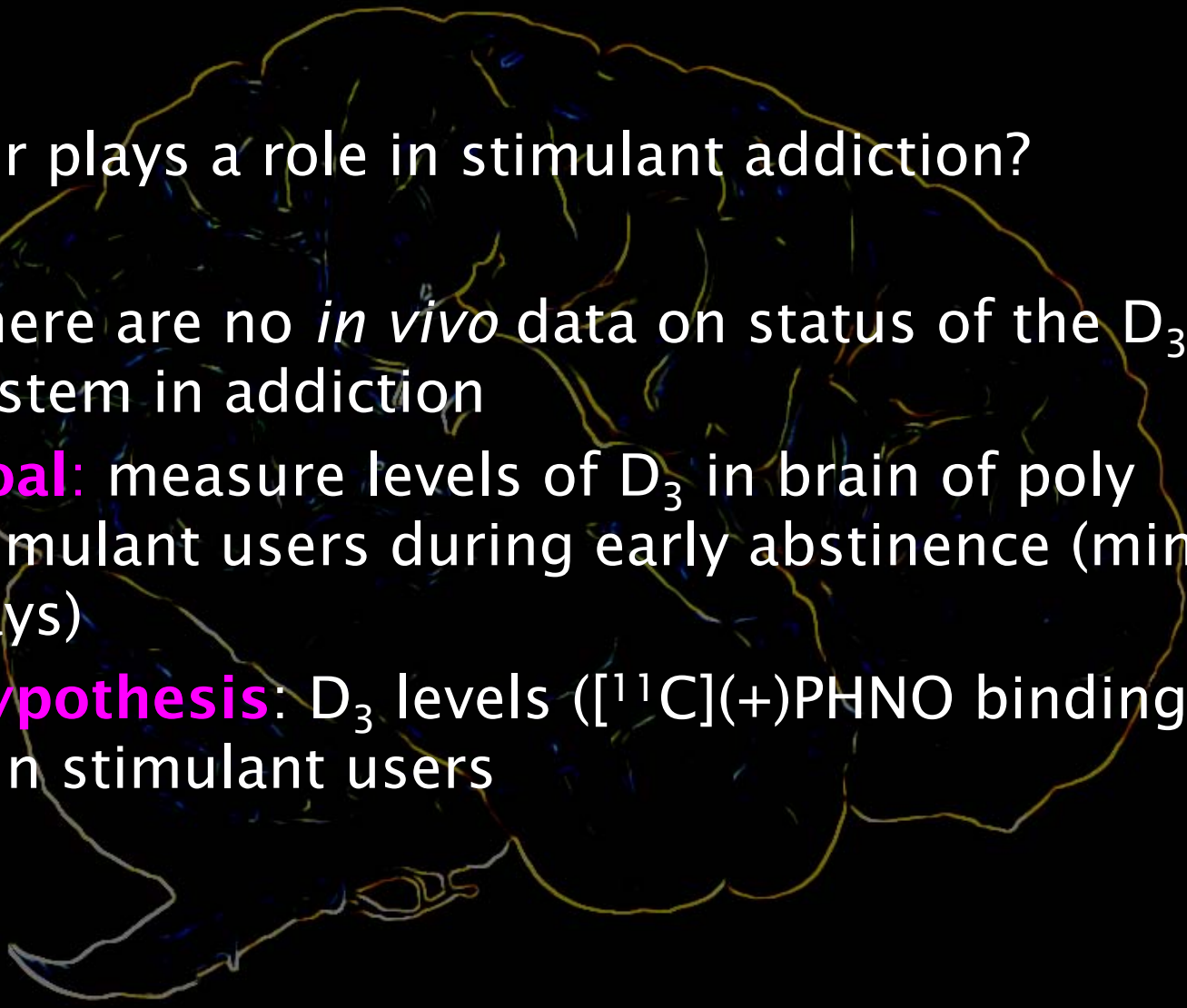
REMARKABLE ectopic up regulation!!

IV

D_3 a plausible candidate for Stimulant addiction?

- D_3 = ↑ density in limbic regions
- D_3 ↑ ↑ ↑ after DAergic stimulation
- D_3 antagonist ↓rewarding/reinforcing actions of drugs / natural reward
  - ↓ ICSS of "reward areas"
  - ↓ cue-induced cocaine SA
  - ↓ stress-triggered cocaine-seeking
  - ↓ cocaine and heroin-induced CPP
  - ↓ alcohol intake and seeking in rats and mice
  - ↓ nicotine-triggered nicotine seeking
  - ↓ cue-triggered sucrose seeking
- D_3 ↑ in cocaine overdose fatalities

AIM of the Study



- D_3r plays a role in stimulant addiction?

- There are no *in vivo* data on status of the D_3 system in addiction
- **Goal**: measure levels of D_3 in brain of poly stimulant users during early abstinence (min.14 days)
- **Hypothesis**: D_3 levels ([^{11}C](+)PHNO binding) are ↑ in stimulant users

Experimental Design

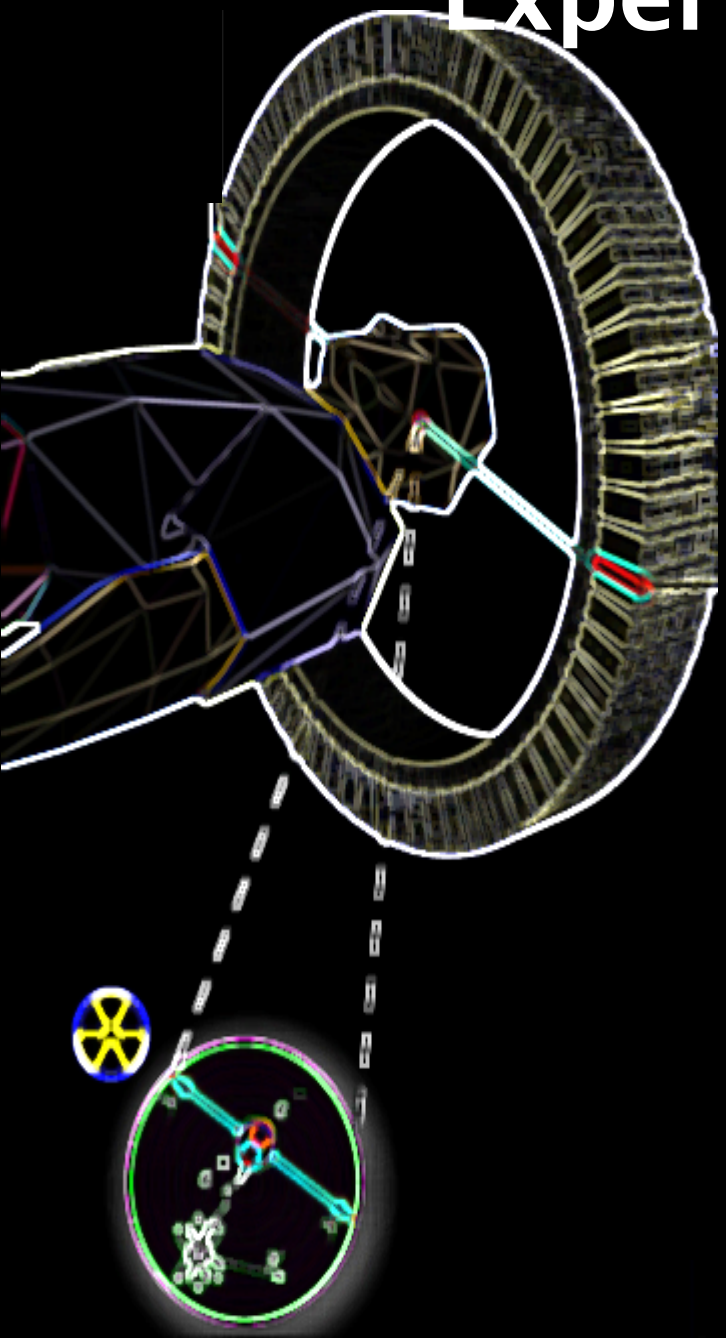
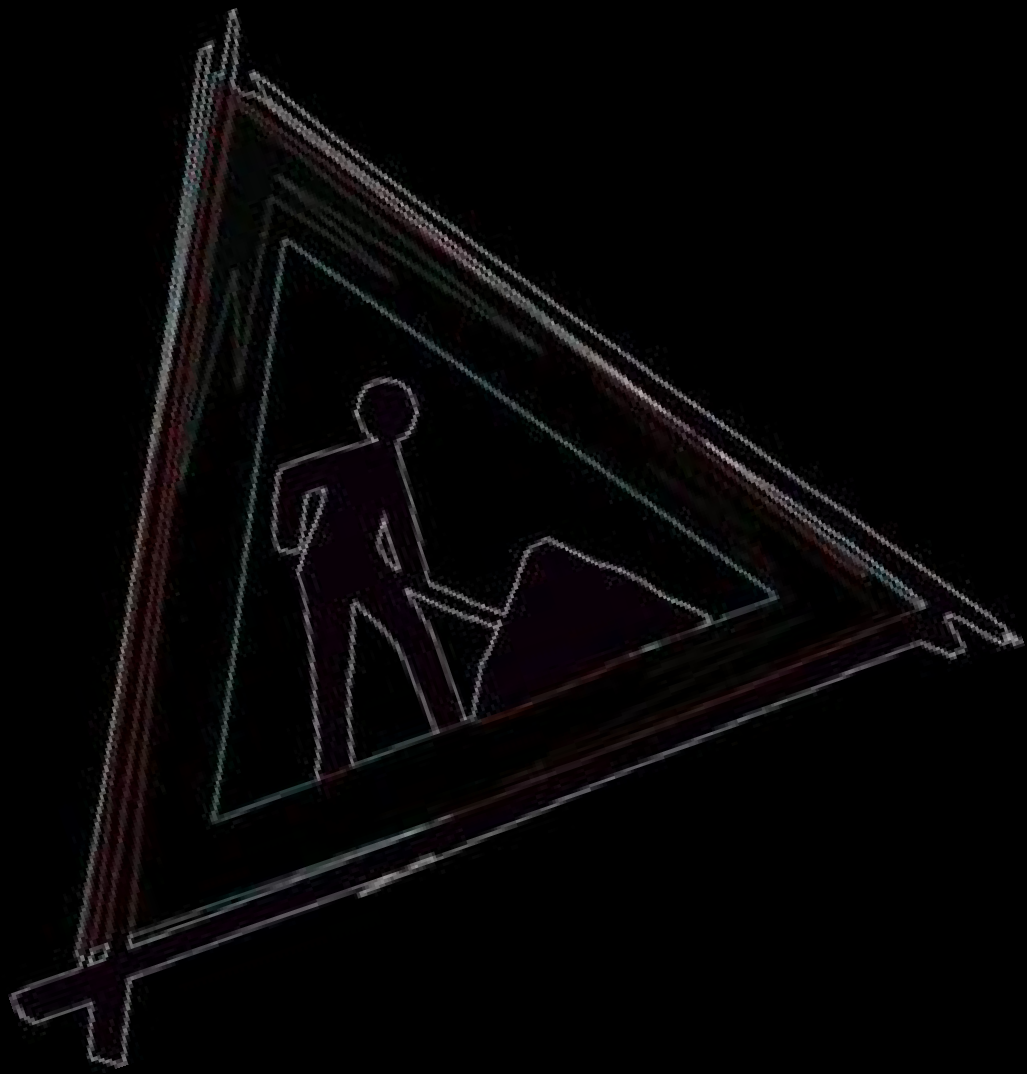


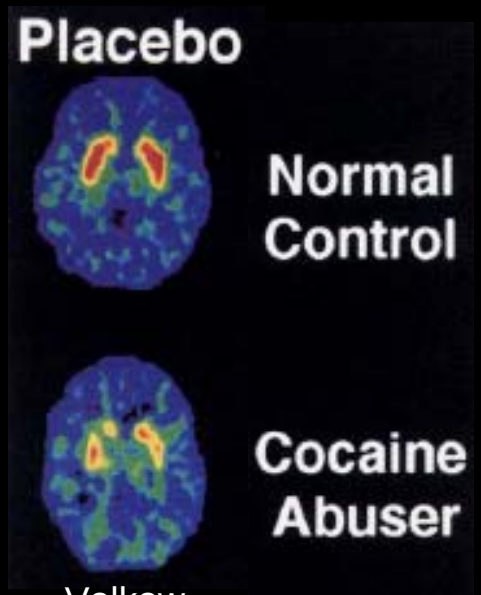
Table 1. Demographic and clinical characteristics of subjects

	Control Subjects	Methamphetamine users	*p*-value
Age	29.7±5.4 years	27.8±5.7 years	0.37
Gender	11 Male/ 3 Female	11 Male / 5 Female	
Ethnicity	11 Caucasian, 2 Asian, 1 Eastern Indian,	13 Caucasian, 2 black, 1 Maghreban	
Education	15.5±2 Years	12.12±2 Years	*0.0001*
Premorbid IQ*	117.1±5.8	117.1±4.9	0.5
Cigarette smokers	5 smokers; 1.7±3 cigarettes/day	9 smokers; 4.5±3 cigarettes/day	0.07
Alcohol use	3±2 drinks/week	4±3 drinks/week	0.19
Years of MA use	N.A.	5.1±3 Years Range: 2-11 years	
Route of administration	N.A.	8 nasal, 3 smoke, 2 nasal/smoke, 2 i.v./smoke, 1 nasal/oral	
Days used- last 30 days	N.A.	5.6±3 days Range: 0-10 days	

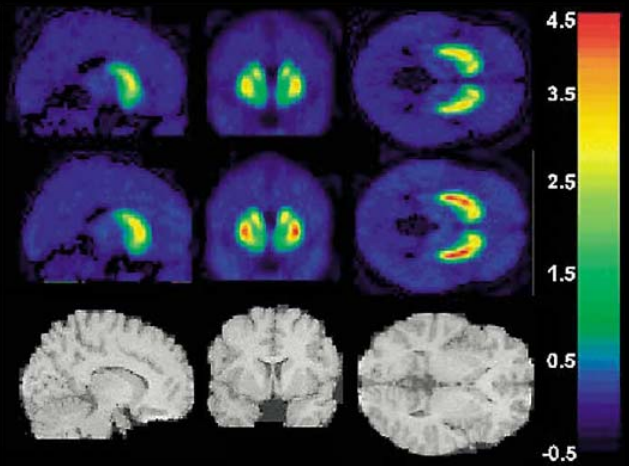
- METH confirmed in hair analysis
- Negative urine on scan day



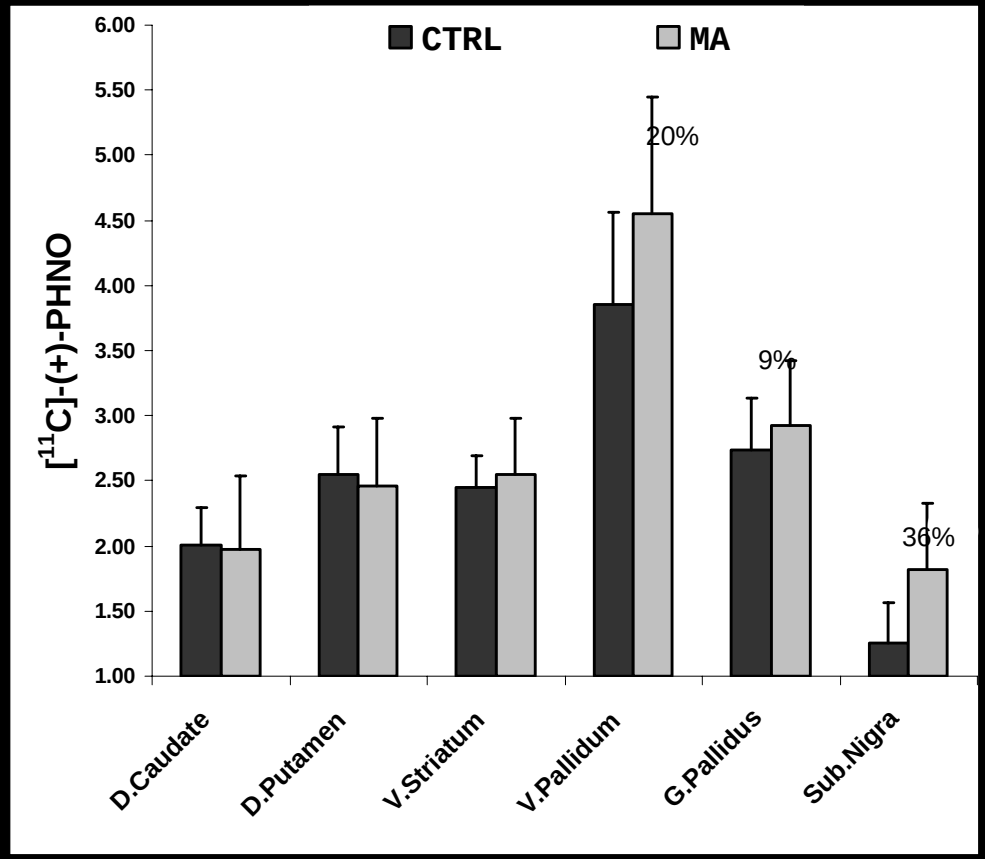
Unlike the finding for D_2, D_3 does not appear to be ↓



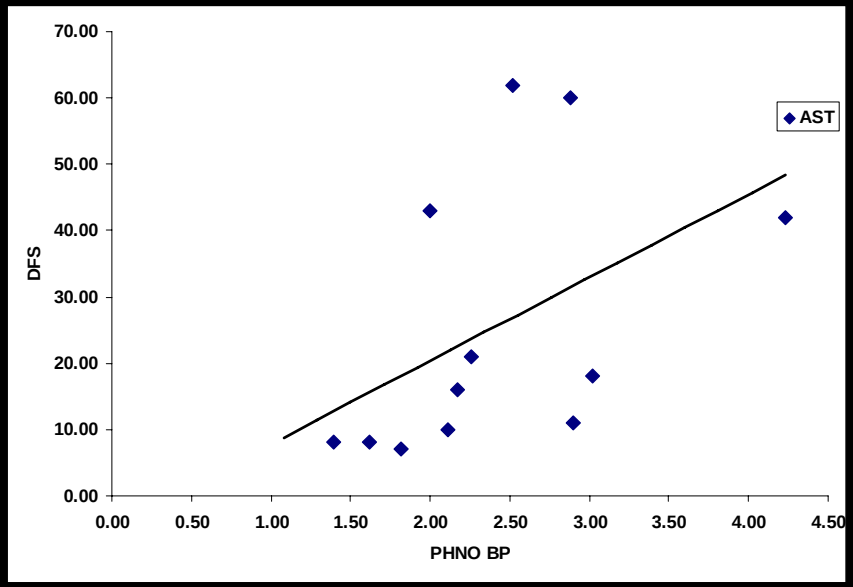
Volkow

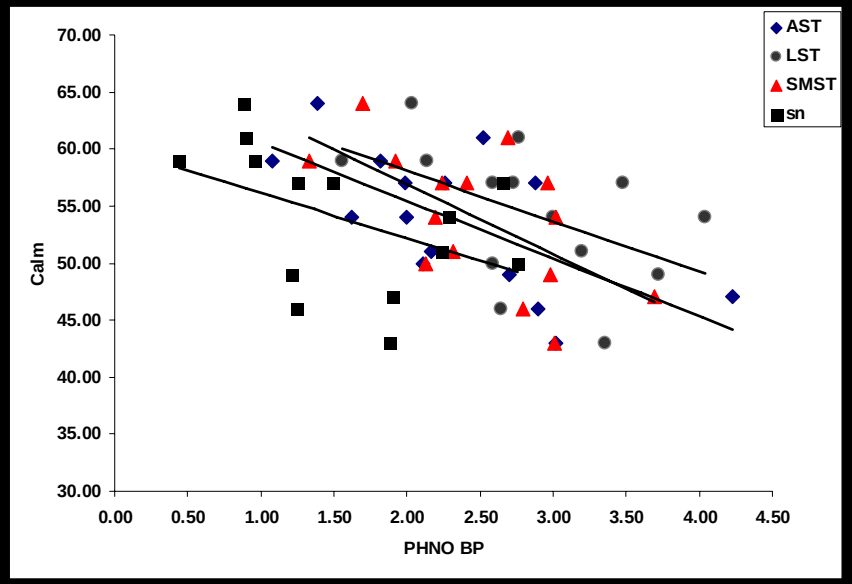


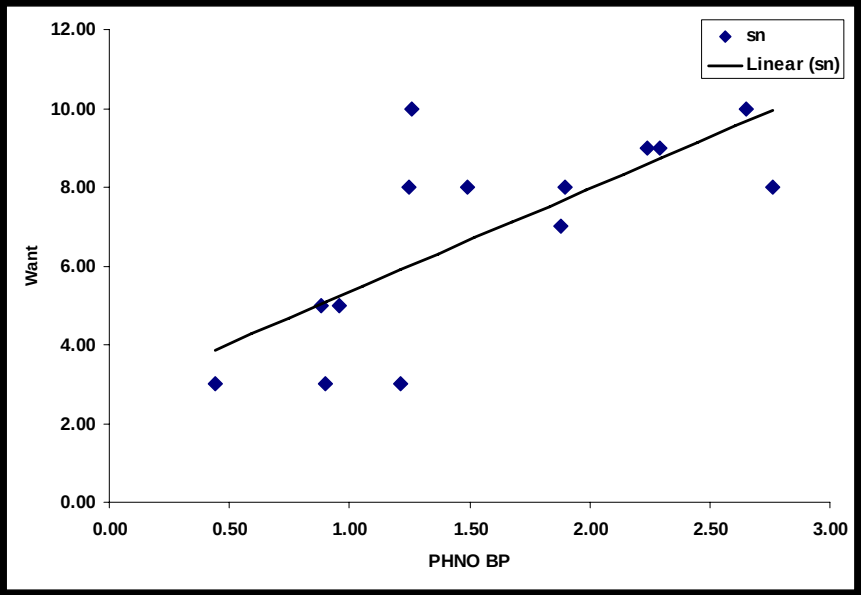
Martinez

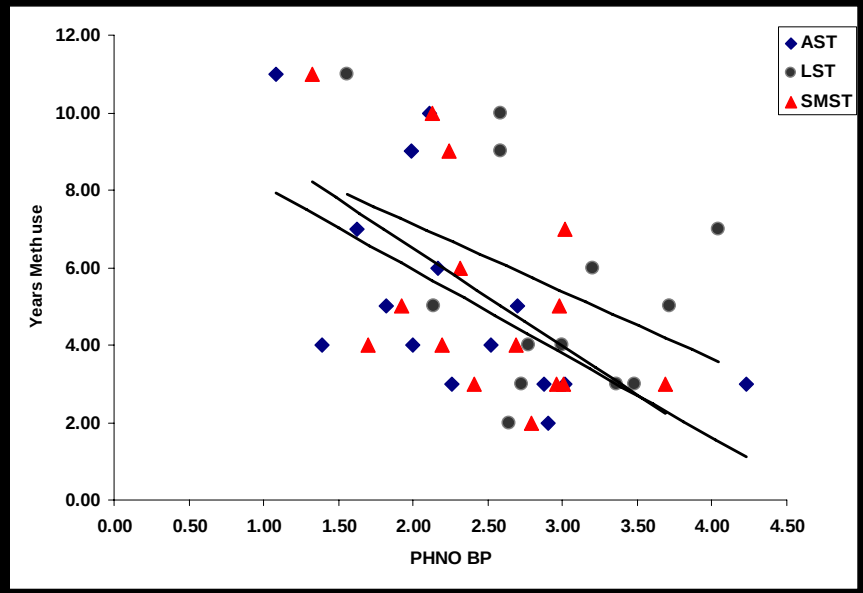


Correlation /Regression



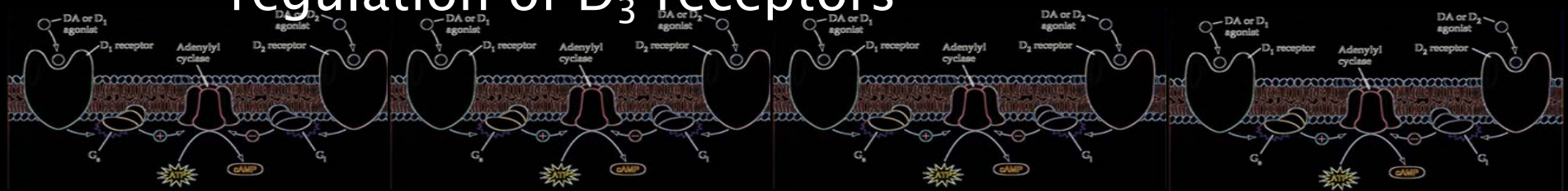






Summary

- D_3 receptor levels ~ ↑ in (+Meth / COC) users
- ↑ binding was related to ↑ drug related *wanting*, *anxiety / mind-racing and self-reported craving*
- ↓ binding in striatal (DC) areas were related to *years of use*
- <u>Does this mean that there is no decrease in D2?</u>
- PHNO binding in dorsal striatum is mostly to D_2: our finding suggest that
  - Users might not be "sever" enough
  - Decreased D_2 was masked by an ectopic up-regulation of D_3 receptors

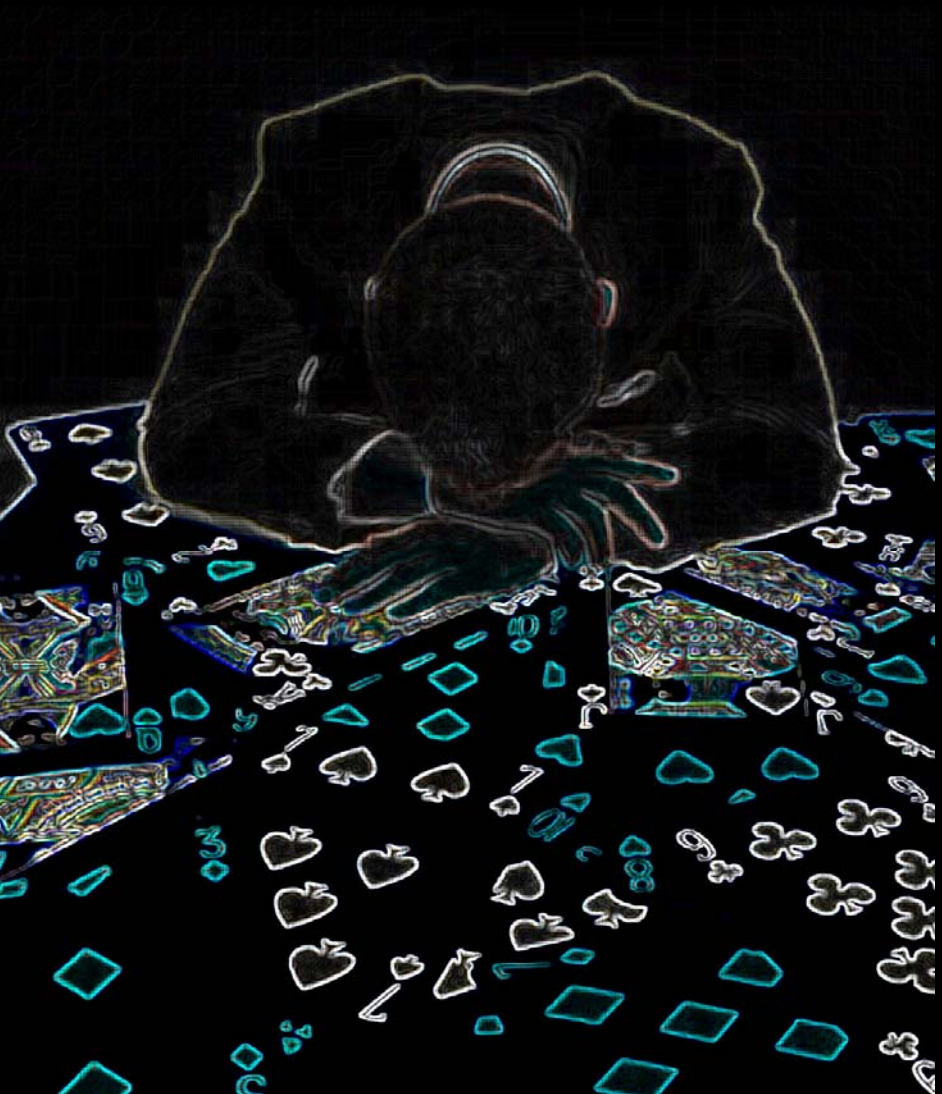


V

Q.: Can changes in D_3r levels explain *sensitization* to DA replacement therapy in PD

Q.: Is the occurrence of ICD (i.e.: *sensitization*) in PD related to D_3

Impulse Control Disorders In PD



ICD: *failure to resist an impulse, drive, or temptation to perform an act that is harmful to the person or others.*

Manifestations include

- Craving and Compulsive use of PD medication
- Pathological Gambling
- Hyper Sexuality
- Compulsive Shopping
- Binge Eating
- Punding / Hobbyism

Are D_3 Preferring Agonists Related to ICD?

Pathological Gambling Caused by Drugs Used to Treat Parkinson Disease

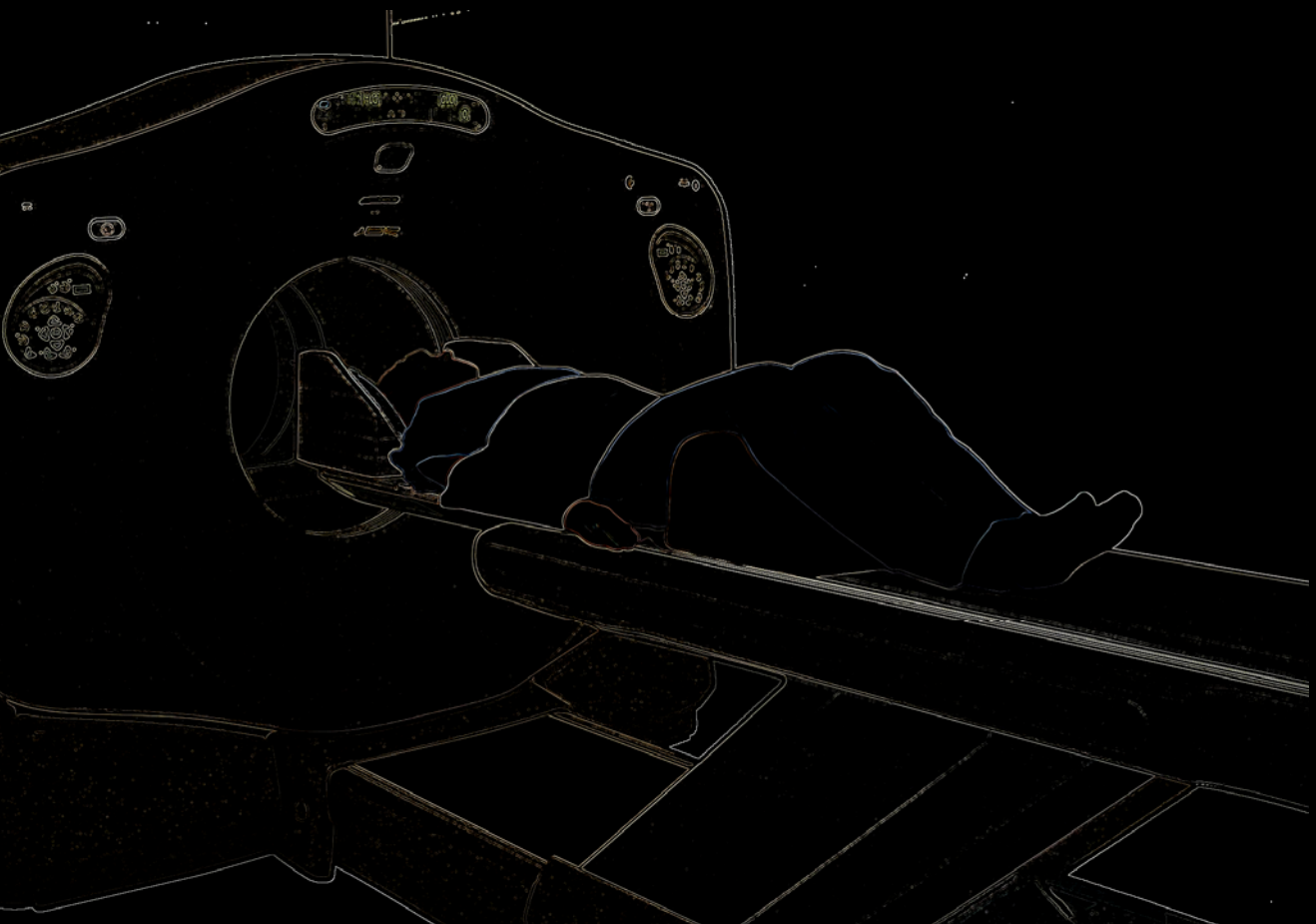
M. Leann Dodd, MD; Kevin J. Klos, MD; James H. Bower, MD; Yonas E. Geda, MD; Keith A. Josephs, MST, MD; J. Eric Ahlskog, PhD, MD

Conclusions: Dopamine agonist therapy was associated with potentially reversible pathological gambling, and pramipexole was the medication predominantly implicated. This may relate to disproportionate stimulation of dopamine D_3 receptors, which are primarily localized to the limbic system.

Arch Neurol. 2005;62:1377-1381

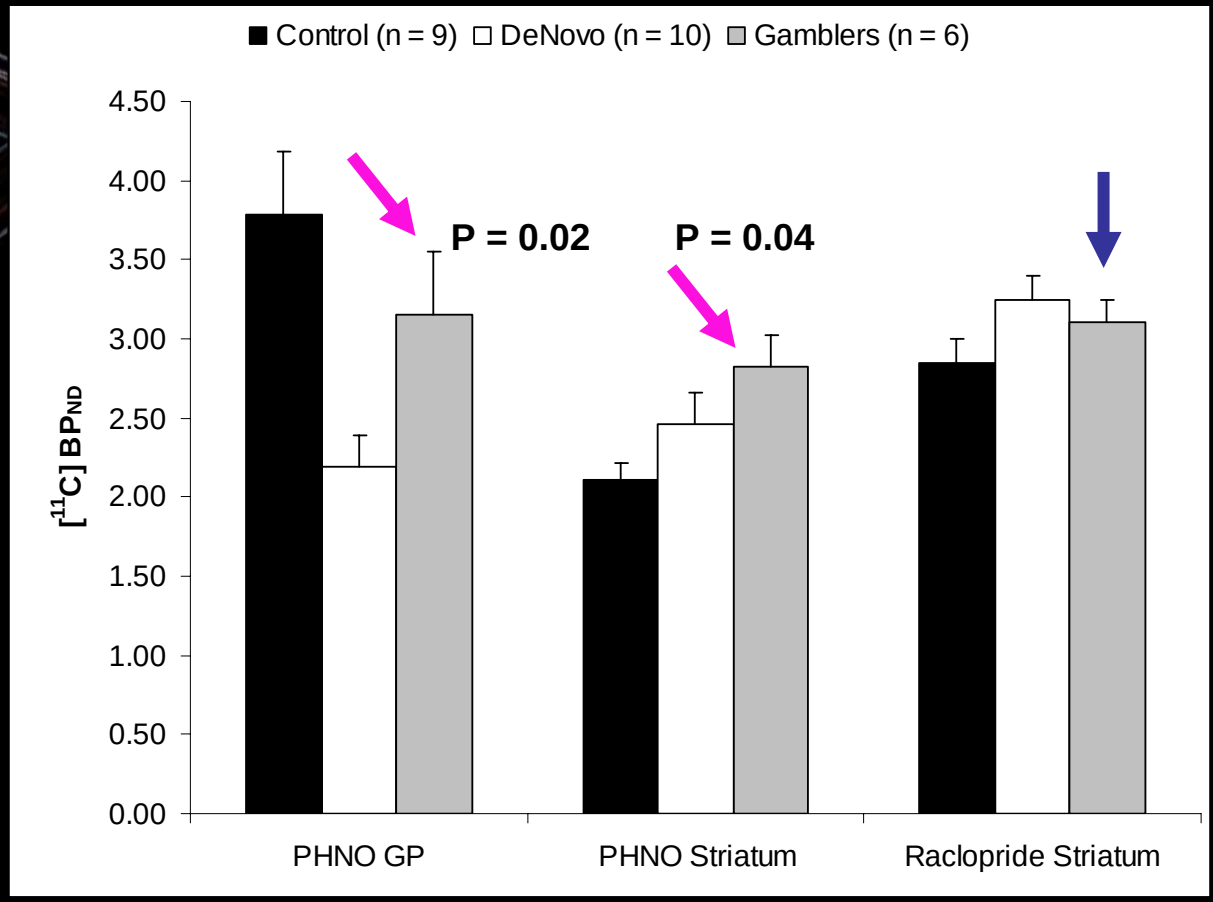
Objective: to compare D_3 ((+)[^{11}C] PHNO) to D_2 (([^{11}C] raclopride) in PD with ICD relative to de novo PD

We expected D_2 to be DOWN and D_3 to be UP!

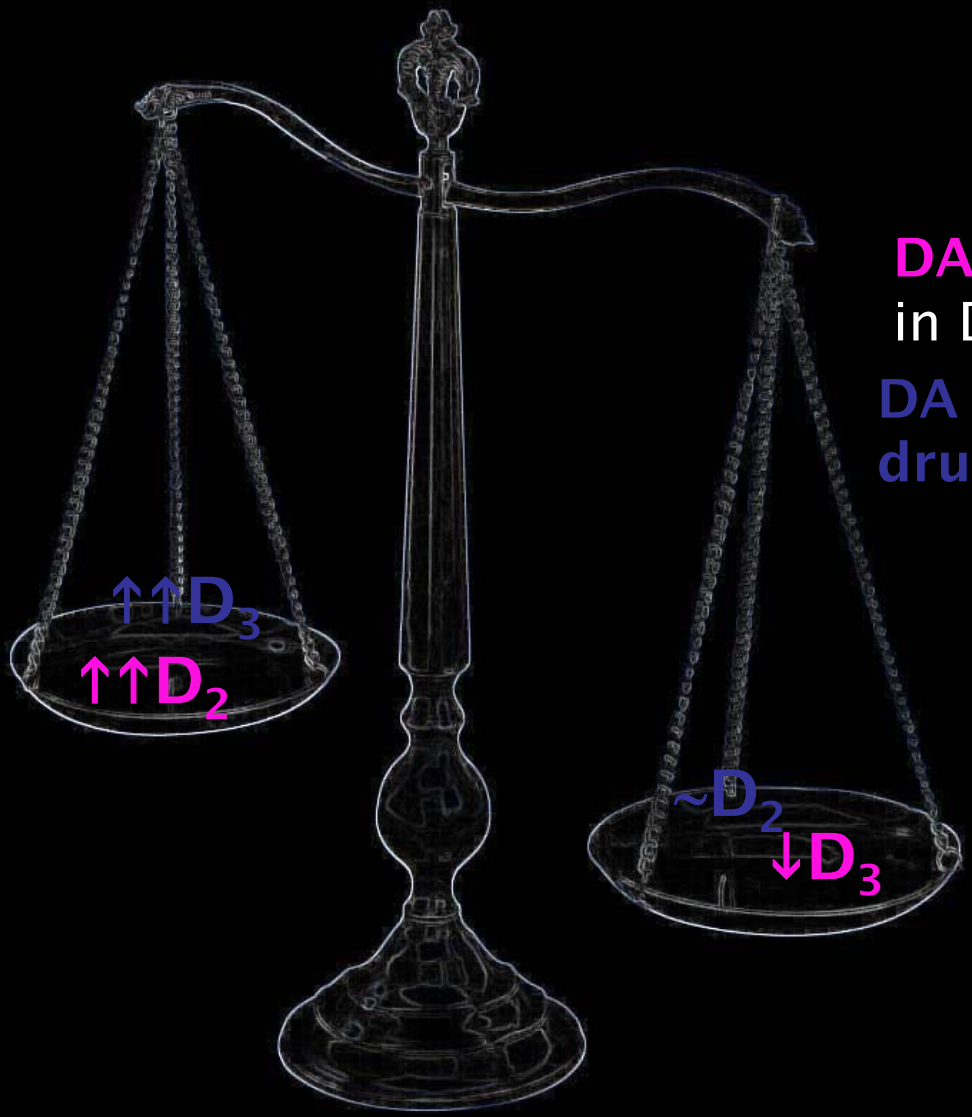


Is D_3 UP in PD with ICD?

SUBJECTS: Age:61; 4M, 2F;PD duration: 8 years, UPDRS 24, Peg Board 9; SOGS: 16, DSM: 13, GA20: 13



Overall Summary



DA Depletion: Differential change in D_2 and D_3

DA stimulation with meds or drugs of abuse: might increase D_3

Future Questions / Conclusion

- Representative sample: Does ↑ D_3 = vulnerability factor for addiction / ICD?
- Addiction pharmacotherapies targeting the D_3 may be more viable:
  - localization of D_3 primarily in limbic areas
  - reinforcing effects of drugs with less motoric side effects
- Preliminary data in line with the rational for testing D_3 receptor blockade as anti-craving agents